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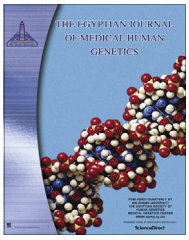

ORIGINAL ARTICLE

Selective screening in neonates suspected to have inborn errors of metabolism

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KEYWORDS

Newborn screening;
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Inborn errors of metabolism;
Selective newborn screening;
Tandem mass spectrometry
MS/MS

Abstract *Background:* Inborn errors of metabolism (IEM) have a high morbidity and mortality in neonates. Unfortunately, there is no nationwide neonatal screen in Egypt, so several cases may be missed.

Objective: The aim of this work was to detect the prevalence of IEM among neonates with suspected IEM, and to diagnose IEM as early as possible in order to minimize morbidity and mortality in high risk neonates.

Subjects and methods: This prospective study included 40 neonates admitted to the Elmahalla General Governmental Hospital Neonatal Intensive Care Unit (NICU) with sepsis like symptoms (lethargy, hypoactivity, poor suckling, and poor crying), convulsions, persistent metabolic acidosis, persistent vomiting, or previous sib death of unidentified cause (neonates with suspected IEM). All included patients were subjected to detailed full history, through clinical examination, laboratory investigations, and metabolic screening by tandem mass spectrometry (MS/MS). Other investigations for IEM including lactate, ammonia, and galactose 1 phosphate levels in the blood, as well as organic acids in urine were done according to each case.

Results: 13 patients (32.5%) were diagnosed as having IEM, 7 of them (53.8%) had urea cycle defect, 2 (15.4%) had maple syrup urine disease, while methylmalonic acidemia, fatty acid oxidation defect, mitochondrial disease, and galactosemia were diagnosed in one patient each (7.7%). Out of these patients, 12 patients (30%) were discharged from NICU after therapy, and one patient (2.5%) died (the one who had mitochondrial disease). Two patients were diagnosed as diseases other than IEM, one had hyperinsulinism and another one had congenital myopathy, while 2 patients were proved to be normal. Five patients (12.5%) were suspected to have IEM (tyrosinemia, mitochondrial

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disease, organic acidemia) 4 of them died before final diagnosis, and one transferred to another NICU. There was a significant difference between diagnosed and undiagnosed patients as regards history of sibling death ($p = 0.012$), plasma ammonia level ($p = 0.002$), and discharge from NICU ($p = 0.000$).

Conclusion: IEM represent a high percent (32.5%) of neonates who had sepsis like symptoms, and when diagnosed, patients showed marked improvement after therapy. IEM should be considered in differential diagnosis of the sick neonates, and investigations, and management should be started rapidly to decrease morbidity, and mortality till nationwide screen for IEM is applied in Egypt.

1. Introduction

Inborn errors of metabolism (IEM) are a highly heterogeneous group of genetic conditions and represent a relevant cause of morbidity and mortality in the pediatric population. IEM, which are individually rare but collectively numerous, are well-recognized entities of the generic class of ''rare'' diseases. Since the first descriptions by Garrod at the beginning of the 20th century, several hundred new disorders have been defined, as new biochemical and molecular diagnostic tools became available [1].

The early diagnosis of IEM by laboratory-based mass screening is a type of preventive medicine. However, several factors restrict the range of IEM that can be screened for, and the number of people to whom it can be made available. Ideally, extension of mass screening of neonates for a clinically significant IEM is a desirable strategy. Tandem mass spectrometry (TMS) is a powerful and effective diagnostic technique and has been proposed as a means to realize this aim. Its main advantages are improved accuracy, sensitivity and specificity over existing methods, and its suitability for cost-effective multidisease IEM mass screening [2].

The aim of this work was to detect the prevalence of IEM among neonates with suspected IEM, and to diagnose IEM as early as possible in order to minimize morbidity and mortality in high risk neonates.

2. Subjects and methods

This study included 40 neonates (31 males and 9 females) admitted to the Elmahalla General Governmental Hospital Neonatal Intensive Care Unit (NICU) with sepsis like symptoms (lethargy, hypoactivity, poor suckling, and poor crying), as well as convulsions, persistent metabolic acidosis, persistent vomiting, or history of previous sib death of unidentified cause, or clinical deterioration in a previously healthy neonate. The study was conducted at the Genetics Unit, Children's Hospital, Ain Shams University, Cairo, Egypt.

The patients' age ranged from 3 to 25 days. All included patients were subjected to detailed full history with special emphasis on age, sex, gestational age, antenatal and perinatal history, symptoms of the patient, age of onset of symptoms, relation of symptoms to feeding, similar cases in the family, parental consanguinity, and previous neonatal death. Through clinical examination, laboratory investigations including complete blood count (CBC), C reactive protein (CRP), electrolytes (Na, K, Ca), blood gases, pH, and metabolic screening by tandem mass spectrometry (MS/MS) were done to detect aminoacid and acyl carnitine profile. Other investigations for IEM including plasma lactate, ammonia level, and organic acids in urine were done according to each case. Galactose 1 phosphate level estimation was done in one patient.

2.1. Statistical methodology

Analysis of data was performed using standard computer program statistical package for social sciences (SPSS) 13.0 for windows (SPSS Incorporation, USA). $P < 0.05$ was considered significant.

3. Results

Thirty-one neonates were males (77.5%). Family history of paternal consanguinity and sibling health of the patients is presented in (Table 1). The weight of the patients ranged from 1.2 to 3.8 kg, with a mean of 2.65 kg ± 0.61 kg. All patients were normal at birth with no complications during delivery, then they started to develop symptoms at an age ranged from 1 to 10 days with a mean of 3.35 ± 2.155 days. The main presenting symptoms were sepsis like symptoms in 25 patients (62.5%) (Table 2). Neurological examination was normal in 12 patients (30%).

Aminoacid and acyl carnitine profile (metabolic screen) by tandem mass spectrometry was abnormal in 13 patients (32.5%), while organic acids in urine showed methyl malonic acidemia in 1 patient (2.5%). The investigations done are shown in Table 3.

Thirteen patients 13/40 (32.5%) were diagnosed as having IEM, out of them 12/13 (92.3%) patients were discharged from NICU after therapy. Urea cycle defect was the commonest IEM diagnosed in 7/13 (53.8%), followed by MSUD in 2/13 (15.4%). 18/40 patients (45%) were not diagnosed as 12/18 (66.7%) of them died and 6/18 (33.3%) of them discharged from NICU before diagnosis. Data are shown in Table 4.

There was no significant difference between diagnosed and undiagnosed patients as regards sex of the patient, age of onset of symptoms, consanguinity, and type of the presenting symptom. There was a statistically significant difference between diagnosed and undiagnosed patients as regards family history of sib death ($p = 0.012$), plasma ammonia level ($p = 0.002$), metabolic screen (aminoacid and acyl carnitine profile) ($p = 0.045$), and fate of the patients ($p = 0.000$).

Seven patients (53.8%) (out of 13 who diagnosed as IEM) had a urea cycle defect. They were full term, and their weight ranged from 1.700 to 3.1 kg. All were normal at birth, and then they started to develop hypoactivity, poor suckling, and poor crying at age ranged between 2 and 7 days. Two of them developed convulsions. Consanguinity of the parents